Al-Mustaqbal University College
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Pathophysiology

Lecture \2

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Cell Damage:

Programmed cell-death (or PCD) is death of a cell in any form, mediated by an intracellular program. PCD is carried out in a regulated process, which usually confers advantage during an organism's life-cycle.

Types of cell damage :

Some cell damage can be reversed once the stress is removed or if compensatory cellular changes occur. Full function may return to cells but in some cases a degree of injury will remain :

Apoptosis or Type I cell-death :

Process of self-destruction of the cell nucleus. It is not contiguous, but instead the dying cells are scattered throughout the tissue. In apoptosis the cells shrink from a decrease of cytosol and the nucleus, but the organelles appear normal. The cell disintegrates into fragments referred to as apoptotic bodies. In the average adult between 50 and 70 billion cells die each day due to apoptosis. Inhibition of apoptosis can result in a number of cancers, autoimmune diseases, inflammatory diseases, and viral infections. Hyperactive apoptosis can lead to neurodegenerative diseases, hematologic diseases, and tissue damage.

Autophagy or Type II cell-death :

Autophagy is generally activated by conditions of nutrient deprivation but has also been associated with physiological as a pathological processes such as development, differentiation, neurodegenerative diseases, stress, infection and cancer .

Macroautophagy, often referred to as autophagy, is a catabolic process that results…in the autophagosomic-lysosomal degradation…of bulk cytoplasmic contents, abnormal protein aggregates, and excess or damaged organelles.

Causes of cell damage :

Physical agents : such as heat or radiation can damage a cell by literally cooking or coagulating their contents.

Impaired nutrient supply : such as lack of oxygen, or the production of adenosine triphosphate (ATP) may deprive the cell of essential materials needed to survive.

The most notable components of the cell that are targets of cell damage are the DNA and the cell membrane :

- **DNA damage**: In human cells, both normal metabolic activities and environmental factors such as ultraviolet light and other radiations can cause DNA damage, resulting in as many as one million individual molecular lesions per cell per day.

- **Membrane damage**: damage to the cell membrane disturbs the state of cell electrolytes, e.g. calcium, which when constantly increased, induces apoptosis.

Regeneration of cell damage:

Regeneration of the parenchymal cells or functional cells of an organism , meaning the body can make more cells to replace the damaged cells keeping the organ or tissue intact and fully functional.

Replacement of cell damage :

When a cell cannot be regenerated the body will replace it with stromal connective tissue to maintain tissue/organ function.

Stromal cells : are the cells that support the functional cells in any organ ; fibroblasts, immune cells, pericytes, and inflammatory cells are the most common types of stromal cells.

Necrosis

Necrosis : is a form of cell injury that results in the premature death of cells in living tissue by autolysis.

Necrosis is caused by factors external to the cell or tissue, such as infection, toxins, or trauma that result in the unregulated digestion of cell components.

In contrast, apoptosis is a naturally occurring programmed and targeted cause of cellular death. While apoptosis often provides beneficial effects to the organism, necrosis is almost always harmful and can be fatal.

Classification :

Structural signs that indicate irreversible cell injury and the progression of necrosis include dense clumping and progressive disruption of genetic material ; and disruption to membranes of cells and organelles.

There are five distinctive morphological patterns of necrosis:

1. **Coagulative necrosis :** is characterized by the formation of a gelatinous substance (gel-like) in dead tissues in which the construction of the tissue is maintained

This pattern of necrosis is typically seen in hypoxic (low-oxygen) environments, such as infarction. Coagulative necrosis occurs primarily in tissues such as the kidney, heart and adrenal glands. Severe ischemia most commonly causes necrosis of this form.

2. Liquefactive necrosis (or colliquative necrosis) : is characterized by the digestion of dead cells to form a viscous liquid mass. This is typical of bacterial, or sometimes fungal infections because of their ability to stimulate an inflammatory response. The necrotic liquid mass is often creamy yellow due to the presence of dead leukocytes and is commonly known as pus.

3.**Caseous necrosis** : can be considered a combination of coagulative and liquefactive necrosis, typically caused by mycobacteria (e.g. tuberculosis), fungi and some foreign substances. The necrotic tissue appears as white and friable, like clumped cheese.

4. **Fat necrosis :** is specialized necrosis of fat tissue resulting from the action of activated lipases on fatty tissues such as the pancreas ; in the pancreas it leads to acute pancreatitis, a condition where the pancreatic enzymes leak out into the peritoneal cavity, and liquefy the membrane by splitting the triglyceride esters into fatty acids through fat saponification.

5. **Fibrinoid necrosis :** is a special form of necrosis usually caused by immune-mediated vascular damage. It is marked by complexes of antigens and antibodies, sometimes referred to as “immune complexes” placed within arterial walls together with fibrin.

Causes of Necrosis :

Necrosis may occur due to external or internal factors :

- External factors : may involve ;

- **Mechanical trauma** (physical damage to the body that causes cellular breakdown).
- Damage to blood vessels (which may disrupt blood supply to associated tissue) and ischemia.
- **Thermal effects** (extremely high or low temperature) can result in necrosis due to the disruption of cells.

- **Internal factors** : causing necrosis include:

 trophoneurotic disorders : injury and paralysis of nerve cells. Pancreatic enzymes (lipases) are the major cause of fat necrosis.

 Necrosis can be activated by components of the immune system, such as the complement system ; bacterial toxins ; activated natural killer cells and peritoneal macrophages.

 Toxins and pathogens may cause necrosis; toxins such as snake venoms may inhibit enzymes and cause cell death.

 Pathogen induced necrosis programs in cells with immunological barriers (intestinal mucosa) may alleviate invasion of pathogens through surfaces affected by inflammation.

Cellular changes of necrosis :

The nucleus changes in necrosis, and characteristics of this change are determined by manner in which its DNA breaks down :

- Karyolysis : the chromatin of the nucleus fades due to the loss of the DNA by degradation.
- Pyknosis : the nucleus shrinks and the chromatin condenses.
- Karyorrhexis : the shrunken nucleus fragments to complete dispersal.

Treatment :

There are many causes of necrosis, and as such treatment is based upon how the necrosis came about :

- Debridement, referring to the removal of dead tissue by surgical ornon-surgical means, is the standard therapy for necrosis. Depending on the severity of the necrosis, this may range from removal of small patches of skin, to complete amputation of affected limbs or organs.
- In the case of ischemia, which includes myocardial infarction, the restriction of blood supply to tissues causes hypoxia and the creation of reactive oxygen species (ROS) that react with, and damage proteins and membranes. Antioxidant treatments can be applied to scavenge the ROS.

 Wounds ; caused by physical agents, including direct physical trauma and injury, can be treated with antibiotics and anti-inflammatory drugs to prevent bacterial infection and inflammation. Keeping the wound clean from infection also prevents necrosis.

- Chemical and toxic agents (e.g. pharmaceutical drugs, acids, bases); react with the skin leading to skin loss and eventually necrosis. Treatment involves identification and discontinuation of the harmful agent, followed by treatment of the wound, including prevention of infection and possibly the use of immunosuppressive therapies such as anti -inflammatory drugs or immunosuppressants.

In the example of a snake bite, the use of anti -venom halts the spread of toxins while receiving antibiotics to impede infection.

Any Question?